

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE 23.Jan.04		3. REPORT TYPE AND DATES COVERED THESIS
4. TITLE AND SUBTITLE "THE EFFECTS OF GENDER ON RECOVERY TIMES FOLLOWING GENERAL ANESTHESIA WITH PROPOFOL AND SEVOFLURANE"			5. FUNDING NUMBERS	
6. AUTHOR(S) CAPT STRAIT SEAN A				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) UNIVERSITY OF TEXAS HSC FT SAM HOUSTON			8. PERFORMING ORGANIZATION REPORT NUMBER CI04-23	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) THE DEPARTMENT OF THE AIR FORCE AFIT/CIA, BLDG 125 2950 P STREET WPAFB OH 45433			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION AVAILABILITY STATEMENT Unlimited distribution In Accordance With AFI 35-205/AFIT Sup 1			12b. DISTRIBUTION CODE DISTRIBUTION STATEMENT A Approved for Public Release Distribution Unlimited	
13. ABSTRACT (Maximum 200 words)				
20040213 058				
14. SUBJECT TERMS			15. NUMBER OF PAGES 69	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT	

**DEPARTMENT OF THE AIR FORCE
AIR UNIVERSITY**

21 January 2004

MEMORANDUM FOR AFIT/CIMI (Maj Russo)

FROM: AFIT/PA Security and Policy Review

SUBJECT: Your Requests for Public Release Approval,
"The Effects of Gender on Recovery Times Following General Anesthesia
with Propofol and Sevoflurane"
By Capt Sean Strait, Capt Dino Dominguez, and Capt Donna Gunning

CASE Number: AFIT/PA Case Number TH040104

1. The thesis above has been reviewed and cleared by AFIT/PA for public release with the following stipulation: please add "disclaimer" clause and remove birth dates and family names in "Vita" section for each author.
2. If you have any questions, please call me at DSN: 785-6565 ext 4379.



PAT WAGNER
Public Affairs Specialist
Air Force Institute of Technology

SECURITY AND POLICY REVIEW WORKSHEET- Request for Public Release Clearance

(In Accordance With AFI 35-101, Chapter 15)

(Do not use this worksheet to request clearance of software or web pages.)

SUBMITTING ORGANIZATION (Office Symbol)

SECSA (AFIT) CIME TH040104

A. DOCUMENT TYPE (Documents must be complete including all figures, charts, photographs and text.)

<input type="checkbox"/> ABSTRACT	<input type="checkbox"/> JOURNAL ARTICLE	<input checked="" type="checkbox"/> THESIS	<input type="checkbox"/> DISSERTATION
<input type="checkbox"/> BROCHURES	<input type="checkbox"/> NEWS RELEASE	<input type="checkbox"/> SPEECH	<input type="checkbox"/> OTHER
<input type="checkbox"/> CD-ROM	<input type="checkbox"/> PHOTO WITH CAPTIONS	<input type="checkbox"/> SUCCESS STORY	
<input type="checkbox"/> DISPLAY/EXHIBIT	<input type="checkbox"/> POSTER SESSION	<input type="checkbox"/> TECHNICAL PAPER	
<input type="checkbox"/> FACT SHEET	<input type="checkbox"/> PRESENTATION WITH TEXT	<input type="checkbox"/> TECHNICAL REPORT	

B. TITLE OF DOCUMENT

The Effects of Gender on Recovery Times following General Anesthesia with

NO. PAGES

69

C. AUTHOR(S) NAME AND DUTY TITLE

Prop. and Sevoflurane
CPT Sean A Strait USAF NC, Nurse Anesthesia Student Primary Investigator
CPT Donna Gunning USAF NC Anesthesia Student CPT Dino Dominguez USAF NC Nurse Anesthesia Student

OFFICE SYMBOL

(AFIT)

D. FORUM (Public release clearance is not required for material presented in a closed meeting and which will not be made available to the general public on the Internet or in any print or electronic media)

DOCUMENT WILL BE <input type="checkbox"/> PRESENTED ORALLY	NAME OF CONFERENCE NA	LOCATION	DATE
DOCUMENT WILL BE <input type="checkbox"/> DISTRIBUTED IN PRINT	NAME OF PUBLICATION NA	SUBMITTAL DEADLINE	

HAVE RELATED DOCUMENTS BEEN PREVIOUSLY CLEARED FOR PUBLIC RELEASE

☒ NO

☐ YES

AFIT CASE NUMBER

NOTE: If document will be released to a medium outside the Department of Defense, the following disclaimer must be added: The views expressed in this article are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the U.S. Government.

FOR AFIT/PA USE ONLY

Thesis is approved with the following stipulations:
Please remove all birth dates and family names in "Vita" sections of each author and add "Disclaimer" clause to document.

SUBMIT TO: Air Force Institute of Technology
Public Affairs (AFIT/PA)
Building 642, Room 2010
2950 P Street
Wright-Patterson AFB OH 45433-7765

FOR MORE INFORMATION

Phone: (937) 255-9354 DSN: 785-9354
FAX: (937) 255-2135 DSN: 785-2135
E-MAIL: afit.pa@afit.edu
WEB: <http://www.afit.mil/newsrm01.htm>

20 JAN RECD

E. NATIONAL SECURITY AND TECHNOLOGY ISSUES

CHECK YES OR NO (Provide a brief explanation for all positive responses in the SYNOPSIS SECTION below.)

- ☐ YES ☒ NO DOES THE MATERIAL HAVE THE POTENTIAL TO BECOME AN ITEM OF NATIONAL OR INTERNATIONAL INTEREST.
- ☐ YES ☒ NO DOES THE MATERIAL AFFECT NATIONAL SECURITY POLICY OR FOREIGN RELATIONS.
- ☐ YES ☒ NO DOES THE MATERIAL CONCERN SUBJECTS OF POTENTIAL CONTROVERSY AMONG DOD COMPONENTS OR WITH OTHER FEDERAL AGENCIES.
- ☐ YES ☒ NO DOES THE MATERIAL CONTAIN TECHNICAL DATA DEVELOPED UNDER CONTRACT OR INDEPENDENTLY DEVELOPED AND CONTROLLED BY THE INTERNATIONAL TRAFFIC IN ARMS REGULATIONS (ITAR) THAT MAY BE MILITARILY CRITICAL AND SUBJECT TO LIMITED DISTRIBUTION, BUT ON WHICH A DISTRIBUTION DETERMINATION HAS NOT BEEN MADE.
- ☐ YES ☒ NO DOES THE MATERIAL CONTAIN INFORMATION ON NEW WEAPONS OR WEAPON SYSTEMS, SIGNIFICANT MODIFICATIONS OR IMPROVEMENTS TO EXISTING WEAPONS OR WEAPON SYSTEMS, EQUIPMENT OR TECHNIQUES.
- ☐ YES ☒ NO DOES THE MATERIAL CONTAIN INFORMATION ON NATIONAL COMMAND AUTHORITIES; COMMAND, CONTROL, COMMUNICATIONS, COMPUTERS AND INTELLIGENCE; INFORMATION WARFARE; OR COMPUTER SECURITY.
- ☐ YES ☒ NO DOES THE MATERIAL CONTAIN INFORMATION ON MILITARY ACTIVITIES OR APPLICATIONS IN SPACE, NUCLEAR WEAPONS, INCLUDING WEAPON-EFFECTS RESEARCH; CHEMICAL AND BIOLOGICAL WARFARE ISSUES; BIOLOGICAL AND TOXIN RESEARCH, HIGH-ENERGY LASERS AND PARTICLE BEAM TECHNOLOGY; ARMS CONTROL TREATY

F. SYNOPSIS (Provide a brief description of the system, process, or technology, including its state of development and whether the application is military, commercial, or dual-use). EXAMPLE: This is new concept of applying current development for high-powered lasers, specifically for military applications.

Describes a study of how gender alters return to consciousness after General anesthesia with Propofol and sevoflurane. All information and references are public.

G. REFERENCES (Check all that apply)

- ☒ ALL REFERENCES ARE UNCLASSIFIED, UNLIMITED, AND ARE AVAILABLE TO THE PUBLIC
- ☐ REFERENCE # ARE SUBJECT TO DISTRIBUTION LIMITATION. NO LIMITED INFORMATION FROM THESE REFERENCES IS INCLUDED IN THE DOCUMENT
- ☐ NO REFERENCES ARE INCLUDED IN THIS DOCUMENT

RELEASE AUTHORITY AND MANAGEMENT RESPONSIBILITY FOR JOINT EFFORTS

IS THIS INFORMATION CO-AUTHORED WITH SOMEONE FROM AN ORGANIZATION OUTSIDE OF AFIT. <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	DOES YOUR ORGANIZATION HAVE THE AUTHORITY TO RELEASE THE INFORMATION <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
IF WORK IS SPONSORED BY ANOTHER ORGANIZATION, DO YOU HAVE THE AUTHORITY TO RELEASE ALL THE INFORMATION <input type="checkbox"/> YES <input type="checkbox"/> NO	IF NOT, WHAT ORGANIZATION SHOULD COORDINATE ON THE REQUEST ORGANIZATION _____ PHONE _____

NOTE: If the organization is a DOD organization, AFIT/PA will coordinate release approval with that organization's PA office

I. AUTHOR/TECHNICAL REVIEW CERTIFICATION	
AUTHOR	
I certify the information contained in the attached document is technically accurate and does not disclose classified, sensitive, or militarily critical technology and does not violate proprietary rights or copyright restrictions. All security and technology issues listed above have been considered and any applicable security classification guides have been reviewed.	
SIGNATURE <i>Sean A. Strait</i>	DATE <i>01/04/04</i>
AUTHOR'S NAME (Print) <i>Capt Sean A. Strait USAF, NC</i> <i>Primary Investigator</i>	TELEPHONE <i>(701) 718 8307</i>
OFFICE SYMBOL/ORGANIZATION <i>AFIT CI</i>	E-MAIL ADDRESS <i>seanstrait@hotmail.com</i>
TECHNICAL REVIEWER CERTIFICATION (Faculty Advisor)	
I certify the information contained in the attached document is technically accurate and does not disclose classified, sensitive, or militarily critical technology and does not violate proprietary rights or copyright restrictions. All security and technology issues listed above have been considered and any applicable security classification guides have been reviewed.	
SIGNATURE	DATE
TECHNICAL REVIEWER'S NAME (Print)	TELEPHONE
OFFICE SYMBOL/ORGANIZATION	E-MAIL ADDRESS
DEPARTMENT HEAD (or equivalent)/PROGRAM MANAGER CERTIFICATION	
The attached material submitted for public release has been properly staffed and reviewed by this division/organization. I support the recommendation of the Author and Technical Reviewer for public release.	
SIGNATURE <i>K. A. Kurelick</i>	DATE <i>13 Jan 04</i>
NAME (Print) KIM A. KURELICK, LT COL, USAF, MSC Associate Dean, Civilian Institution Programs	TELEPHONE <i>255-2259 X3020</i>
OFFICE SYMBOL/ORGANIZATION <i>AFIT/CI/MT</i> Force Institute of Technology	
AFIT PUBLIC AFFAIRS	
THE ATTACHED MATERIAL IS IS NOT CLEARED FOR PUBLIC RELEASE	
SIGNATURE OF SECURITY AND POLICY REVIEW OFFICER <i>Pat Wagner</i>	DATE <i>21 Jan 04</i>
J. REMARKS (please reference the specific section) <i>Pat,</i> <i>Please Forward Approval Notice to</i> <i>Tamiko. Alexander@afit.edu. Lt COL Kurelick</i> <i>Signed in the Absence of Major Kissel.</i> <i>Thanks</i> <i>Tamiko</i>	

**THE VIEWS EXPRESSED IN THIS ARTICLE ARE THOSE OF THE AUTHOR
AND DO NOT REFLECT THE OFFICIAL POLICY OR POSITION OF THE
UNITED STATES AIR FORCE, DEPARTMENT OF DEFENSE, OR THE U.S.
GOVERNMENT**

ABSTRACT

Research has shown that men and women metabolize drugs differently, but little is known about how gender affects recovery from general anesthesia. The purpose of this study was to determine if there were differences in recovery times between men and women following general anesthesia with sevoflurane and propofol. A review of the literature showed two studies where women awoke from general anesthesia significantly faster than men.

Following institutional review board approval, 24 men and 24 women were enrolled in this descriptive, non-randomized, quasi-experimental study. After informed consent was obtained, general anesthesia was induced with a standardized weight-based protocol. Anesthesia was then maintained with a propofol infusion and sevoflurane was adjusted to maintain appropriate anesthetic depth. Following discontinuation of anesthetic agents, recovery end points (eye opening and hand grip) were elicited by investigators at one-minute intervals. For the purposes of the study the subject was considered recovered when both end points were met.

There was no statistically significant difference in demographics, or type of surgery. No statistically significant difference was found in recovery times between the two groups.

This study did not control for local anesthetic injections made by the surgeon that might influence recovery times. Because women continue to experience recall at higher rates than men more studies are needed in this area.

THE EFFECTS OF GENDER ON RECOVERY TIMES FOLLOWING GENERAL
ANESTHESIA WITH PROPOFOL AND SEVOFLURANE

By

Sean A. Strait, B.S.N.

Dino R. Dominguez, B.S.N.

Donna T. Gunning, B.S.N.

A Cluster Research Proposal

Submitted in partial fulfillment of

the requirements for the degree of

Master of Science in Nursing

The University of Texas Health Science Center at Houston

School of Nursing

December, 2003

TABLE OF CONTENTS

	Page
ABSTRACT.....	ii
CONTENTS.....	iii
THESIS SIGNATURE SHEET.....	v
HUMAN SUBJECTS LETTER OF APPROVAL.....	vi
LIST OF TABLES.....	vii
LIST OF FIGURES.....	viii
CHAPTER	
I Introduction.....	1
Statement of the Problem.....	2
Significance of the Problem.....	3
Theoretical Framework.....	6
Consciousness Theory.....	6
Purpose.....	8
Definition of Terms.....	8
Research Question.....	9
Assumptions.....	9
Limitations.....	10
Summary.....	10
II Review of Related Literature.....	12
Pharmacokinetics and Pharmacodynamics.....	12
Sevoflurane.....	21
Propofol.....	23
III Methodology.....	29

Population, Sample, and Setting.....	29
Instrumentation.....	31
Data Collection Tool.....	32
Respiratory Gas Monitor.....	32
Procedure for Data Collection.....	33
Protection of Human Subjects.....	36
Study Design.....	37
Procedure for Data Analysis.....	38
IV Analysis of the Data.....	39
Description of the Sample.....	39
Findings.....	40
V Discussion, Conclusions, Implications, and Recommendations.....	42
Discussion.....	42
Conclusions.....	47
Implications for Nursing.....	47
Recommendations for further Research.....	48
APPENDICES	
A Data Collection Tool.....	49
B Informed Consent Document.....	52
REFERENCES.....	58
VITAE.....	67

THE EFFECTS OF GENDER ON RECOVERY TIMES FOLLOWING GENERAL
ANESTHESIA WITH PROPOFOL AND SEVOFLURANE

By

Dino R. Dominguez, B.S.N.

Donna T. Gunning, B.S.N.

Sean A. Strait, B.S.N.

APPROVED:

Ch. Lett 7 B-ly PDRN CENS
Brian A. Clay, MSN
SD, MS

59th Medical Wing (Wilford Hall Medical Center)
Institutional Review Board (IRB)
59th Clinical Research Squadron
Protocol Support/MSRP/(210) 292-7143
1255 Wilford Hall Loop, Lackland AFB, TX 78236-5319

FINAL IRB APPROVAL

12 Jul 02

Approval Date: 25 Jun 02

Principal Investigator: LTC Elizabeth Bridges/MSR

IRB Reference Number: FWH20020108H

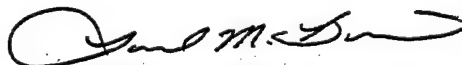
Protocol Title: "Gender Differences In Recovery from Propofol and Sevoflurane Anesthesia"

1. Your study, referenced above, has received final approval by the Wilford Hall Medical Center's Institutional Review Board (WHMC/IRB). Additional items reviewed and approved by the WHMC/IRB include:

Informed Consent (ICD) dated 25 Jun 02
Data Collection Tool*

You are required to sign the protocol a second time to initiate your study. Please stop by the Protocol Office to accomplish this required tasking.

2. In order to start your study you must contact the Protocol Office at 2-7143/2-7184 as soon as possible to schedule a "New Study" start-up meeting. You will be given a study binder, original stamped ICD, and any other documents you will need.
3. Your minimal risk study will be forwarded to the Surgeon General's Research Oversight Committee for concurrence.
4. The WHMC/IRB must be notified immediately of any additional information, or changes to the protocol. All amendments to either the protocol or ICD must be reviewed and approved by the WHMC/IRB prior to their inception.
5. You must comply with the information contained in the Research CD (Investigator Brochure) and your Certificate of Compliance.
6. It is the WHMC/IRB's decision that this study will be terminated as of 24 Jun 03 unless you submit a progress report, using the template provided on your research CD (Human Progress Report 2002). Your first progress report, which is a request for continuation of the study, will be due to the Protocol Office no later than 1 May 03. A progress report will be due every 11 months thereafter, in order for the WHMC/IRB approve continuance of the study for another year. Upon completion of your study you must submit a final report.



LAMOND M. BARNES, SSgt, USAF
NCOIC, Protocol Support

1 Attachment:
ICD Instructions

LIST OF TABLES

Table	Page
1 Gender Distribution of ASA Status and Age.....	40
2 Gender Distribution of Surgery Types.....	40
3 Median Times to Eye Opening.....	41

LIST OF FIGURES

Figure	Page
1 Theoretical Framework Model.....	6

CHAPTER 1

Introduction

Many studies using animal and human models have shown that gender affects drug function. Even so, women were not routinely included in pharmacologic research. In 1993 the Food and Drug Administration (FDA) stated that women should be included in clinical drug trials (Merkatz, Temple, Sobel, Feiden, & Kessler, 1993). Despite this mandate, little is known about how gender affects recovery time from general anesthesia. Studies showing significant decreases in recovery time for men or women could have an impact in civilian and military anesthesia.

Patient safety, patient comfort, and cost containment are the impetus for much of the research conducted by anesthesia providers (Pasternak, 1998). Song, Girish, & White, (1998) found that the use of shorter-acting intravenous agents and potent inhalation drugs decreased recovery time from general anesthesia. Following the use of these newer agents, such as sevoflurane and propofol, patients spend less time in the post anesthesia care unit (PACU), generally experience less postoperative discomfort and nausea, and are discharged home earlier (Peduto, Mezzetti, Properzi, & Giorgini, 2000). Additionally, patients report a high degree of satisfaction with ambulatory surgery associated with the use of the newer anesthetic agents, and hospitals receive financial benefits

from decreased PACU workload and length of stay.

Wartime anesthesia shares many of the goals of civilian anesthesia, but quick recovery and fast turnover times take on special significance. During war, patients must be moved out of the operating suite as fast as possible to make room for the next casualty. Any technique that can decrease operating room turnover time and allow PACU personnel to safely care for more patients will enhance medical readiness and contribute to a successful mission. Drugs the anesthesia provider chooses to use during the administration of general anesthesia influences the rate of recovery. Multiple factors including the type of surgery and patient demographics, specifically gender, have been found to play a role (Pavlin et al., 1998).

Statement of the Problem

The purpose of this study was to determine if there were differences in recovery times between men and women following general anesthesia with sevoflurane and propofol. Rapid recovery and discharge from the operating room is important to maximize operating room time and conserve material and personnel resources. Therefore, recovery time must be considered when administering a general anesthetic. While there is an abundance of research on differing recovery profiles for given anesthesia agents and types of

surgery, little is known about how gender affects overall recovery time.

Significance of the Problem

As a result of the FDA mandate that women should be included in clinical drug trials, researchers have concluded that gender differences affect the pharmacokinetics and pharmacodynamics of various drugs. For example, women received better pain control following administration of pentazocine (Talwin®) than did males (Gear et al., 1996). Pain control following surgery can be optimized if anesthesia providers consider identified gender responses to pain therapy. Vuyk, Oostwouder, Vletter, Burm, & Bovill, (2001) found that the pharmacokinetics of propofol was significantly ($p < .05$) affected by gender. Women were found to have a higher metabolic clearance of propofol, but a decreased peripheral clearance. The authors suggest that lower cardiac output and higher body fat percentages of females compared to males may explain the differences. Furthermore, the differences may explain why women have been found to recover from general anesthesia faster than men. These results point to the need to administer propofol to women

at an approximately 10% higher infusion rate than men (Vuyk et al., 2001).

Certain hormones and proteins vary between the sexes. Harris, Benet, & Schwartz, (1995) state that α_1 -acid glycoprotein (AAG) concentration can be decreased by endogenous estrogen. Therefore, women may exhibit decreased AAG plasma concentrations. Because many drugs used in anesthesia undergo AAG binding, this finding may affect the way men and women recover from general anesthesia. However, neither propofol nor sevoflurane appear to be affected by AAG binding.

During a multi-center study designed to evaluate bispectral index, intraoperative management, and patient recovery, researchers unexpectedly discovered that women emerged from general anesthesia with propofol, alfentanil, and nitrous oxide significantly faster ($p < .001$) than men (Gan et al., 1999). Gan et al suggested that women may exhibit a decreased response to the same dose of a drug and therefore awaken more rapidly from general anesthesia. Myles, McLeod, Hunt, & Fletcher, (2001) found a significantly shorter time ($p = .024$) to emergence for

women after general anesthesia but not a shorter time to discharge from the recovery room. It has been suggested that a shorter recovery time from general anesthesia may explain, in part, why women experience awareness during surgery at a higher rate than men. An analysis of closed medical malpractice cases from 1961 to 1995 revealed that awareness claims against anesthesia providers accounted for 1.9% of all claims. Seventy-seven percent of claims involved women 60 years of age or younger, ASA class I-II, who had elective surgery (Domino, Posner, Caplan, & Cheney, 1999).

It is possible that there is a difference in the way men and women respond to all drugs. It is important to determine if differences exist in order to choose agents and techniques that will provide optimal anesthesia and recovery profiles.

This study enrolled subjects from a convenience sample of patients who presented to a U.S. Air Force medical facility for surgery. The patients enrolled received general anesthesia with sevoflurane and a propofol infusion. The anesthetic regimen for each subject was guided by a preoperative evaluation and was designed to

optimize each subject's physiological and psychological state; no subject's anesthetic plan was changed to support the assumptions or purpose of the study.

Theoretical Framework

The framework for this study is the theory of consciousness (Figure 1). Consciousness is a broad term for a complicated brain phenomenon that deals with self-awareness and environmental interactions. Young and Pigott, (1999) describe several subdivisions of consciousness that work together to form a picture of the world in humans.

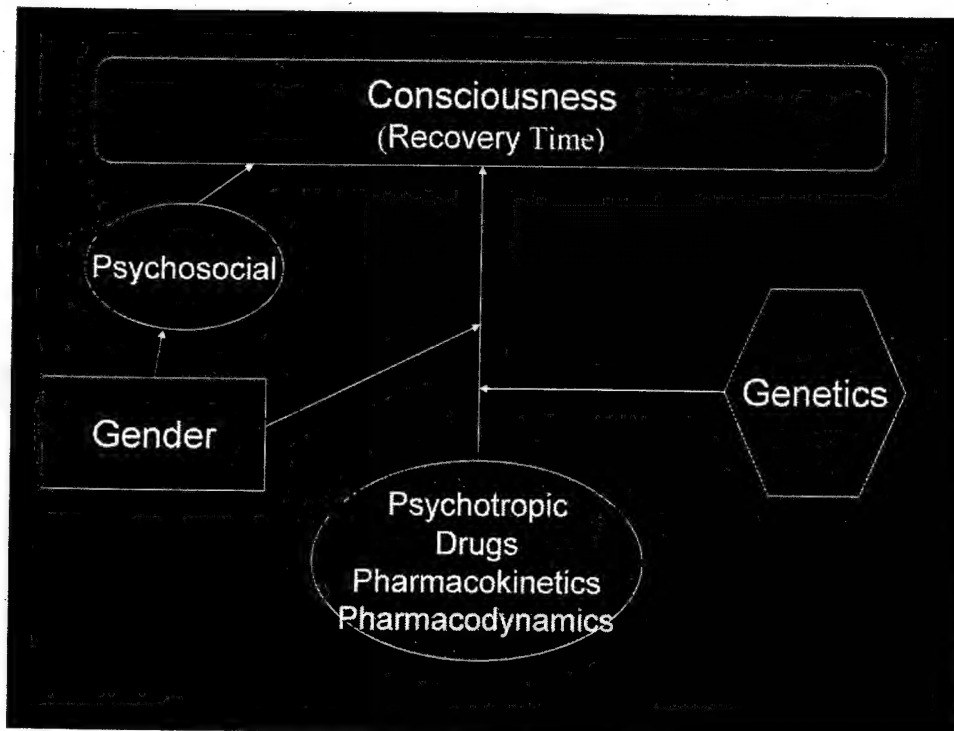


Figure 1. Theoretical framework model.

The major subdivisions are as follows: alertness, attention, memory, the motivational system, and cognition. Alertness is the quality of paying attention to, or the readiness to respond to, a stimulus. Attention is concentrating on an environmental feature. Memory is retention of ideas and experiences. Motivation represents the impetus for action in response to thoughts or stimulation (Stedman, 2002). Finally, cognition is the mental processes (awareness, reasoning, and judgment) by which knowledge is acquired (Thomas, 1989).

This study focused on whether gender affects time of return to consciousness after anesthesia. Only early recovery from general anesthesia was measured. This study did not evaluate other indicators of recovery such as discharge times from PACU. Early return to consciousness (recovery from general anesthesia) was measured by the subject's ability to both open his or her eyes and grip and release the investigator's hand when instructed to do so. End-agent sevoflurane concentration values were also collected and recorded at five-minute intervals throughout the case, but were not considered end points for recovery in this study.

Purpose

The purpose of this study was to determine if gender effects recovery time from propofol and sevoflurane anesthesia in adult patients.

Definition of Terms

Emergence. Conceptual definition: Recovery of function after unconsciousness, often associated with general anesthesia (Pugh, 2000). Operational definition: The time to initial eye opening on command, following cessation of all anesthetic agents.

End-Tidal Agent Concentration. Conceptual definition: The quantification of exhaled sevoflurane in the anesthesia circuit reflective of alveolar gas concentrations. Operational Definition: The end agent concentration of sevoflurane was measured using the Ohmeda 5250 respiratory gas monitor. End-agent concentrations were recorded on the data collection tool at five-minute intervals.

Gender. Conceptual definition: Categorical placement based on male or female sex (Pugh, 2000). Operational definition: Patients were stratified into one of two categories based on whether they were male or female.

General anesthesia. Conceptual definition:

Unconsciousness and loss of ability to perceive pain associated with inhalation and/or intravenous anesthesia (Pugh, 2000). Operational definition: Anesthesia with unconsciousness, induced and maintained with sevoflurane and propofol. Patients were either spontaneously breathing or assisted with ventilation.

Recovery time. Conceptual definition: "Emergence from general anesthesia." (Pugh, 2000, p. 1534). Operational definition: The time period from the discontinuance of anesthesia until the patient spontaneously opened their eyes and the time until the patient could follow the command to squeeze and release the fingers of the investigator.

Research Question

Does gender affect recovery time following general anesthesia with propofol and sevoflurane?

Assumptions

The assumption for this study was:

Recovery time from general anesthesia is effected by gender unique differences in pharmacokinetics and pharmacodynamics.

Limitations

The limitations of this study were:

1. The study was a convenience sampling of military members and their dependents and therefore, may not be generalizable.
2. Administering additional drugs, such as muscle relaxants or opioids, may have altered recovery times.
3. The type and duration of the surgical procedure may have affected recovery times.
4. Any significant results identified with a sevoflurane and propofol combination are not generalizable to other general anesthetic agents.
5. Statistically significant recovery times between men and women may not be clinically significant.
6. This study was not designed to determine causative factors for any significant results.

Summary

The rate at which patients recover from general anesthesia determines when they are discharged from the PACU and when they are able to return home. Recovery time is influenced by multiple factors including the type of anesthesia, type of surgery, and gender. Little information

exists about how gender affects recovery time. This study attempted to determine if gender influences recovery time from sevoflurane and propofol general anesthesia.

CHAPTER II

Review of Related Literature

This study was designed to determine if gender affects recovery time from sevoflurane and propofol anesthesia.

Many factors can affect the pharmacokinetic and pharmacodynamic reaction to drugs and influence recovery from general anesthesia.

Pharmacokinetics and Pharmacodynamics

The mechanism of action of anesthetic drugs is poorly understood and many factors contribute to individual variations in emergence from anesthesia. However, all drug actions in the body are governed by the principles of pharmacokinetics and pharmacodynamics. Pharmacokinetics is "the study of what the body does to a drug" and pharmacodynamics is "the study of what the drug does to the body" (Shafer, 1998). The principles of pharmacodynamics and pharmacokinetics must be considered during any study that focuses on drugs and their effects on the human body.

Two key pharmacokinetic principles are volume of distribution and clearance. Volume of distribution is drug movement from the point of entry in the body to the organs and tissues. Clearance is the body's ability to remove the

drug from the blood or plasma and is usually expressed as an amount of drug removed per unit of time (Shafer, 1998). Gender can influence pharmacokinetics. For example, women secrete less gastric acid and have slower gastric emptying than men (Belerle, Meibohm, & Derendorf, 1999). This difference can alter the times of absorption, onset, and elimination of oral medications. Seaber et al., (1997) found that Zoltriptan had a decreased volume of distribution in men as compared to women, although they could not document a clinical difference. Both volume of distribution and clearance are important concepts to consider as recovery time from general anesthesia is studied.

Pharmacodynamic components, specifically receptor-ligand interactions, are also important concepts to consider. As described by Shafer, (1998) the gamma amino butyric acid (GABA_A) macromolecule receptor is a ligand activated chloride ion channel. When activated, by GABA, the receptor allows a flux of chloride into the neuron resulting in hyperpolarization and prevention of neural tissue depolarization. Propofol is a general anesthetic that functions through the GABA_A receptor.

Several theories have been proposed to explain the functioning of potent inhalation anesthetics. The Unitary Theory proposes that all general anesthetics have the same mechanism of action. Conversely, the Degenerate Theory suggests that each class of general anesthetic works through an independent mechanism (Miller & Alifimoff, 1998). Just as there is dissension about how the general anesthetic agents function, where they work is also in question. Miller & Alifimoff, (1998) discussed three probable sites of action for general anesthetics: cellular proteins, the lipid bilayer of cellular membranes, and the lipid protein interface. Given the lack of knowledge about how and where potent inhalation agents work, it is not surprising that little information is available concerning gender specific affects of these agents.

Although this study will focus on how gender affects recovery time from anesthesia, other possible factors need to be described briefly. These other possible influences include genetics, socialization, age, and hormone levels.

Genetics has a strong influence on how an individual responds to drugs including anesthetics and anesthetic adjuvants. Malignant hyperthermia is known to be related to

genetic alterations in ryanodine receptors in humans (Keating et al., 1997). Collins et al., (2000) studied recovery from rocuronium in 36 Caucasian and Chinese women and 36 Caucasian and Chinese children. They found rocuronium duration was significantly longer ($p < .05$) with a 10 minute difference in adults and 6 minute difference in children for both Chinese and Caucasian adults and children. However, the study was limited by a small sample size. In a study comparing recovery times from remifentanyl and propofol anesthesia, Ortolani et al. (2001) found that Senegalese African Blacks took longer to recover than Italian Caucasians.

Studies have shown age to be a factor in patient responses to drugs. Greenblatt et al., (1984) compared midazolam kinetics in young (24-37 yrs) and older (60-79 yrs) men and women. Their study showed a statistically significant increase ($p < .01$) in midazolam elimination half-life and decreased clearance in older males compared to younger males. Comparisons of the female groups showed similar but not statistically significant results. Altered elimination and increased half-life of a drug such as midazolam can affect consciousness and recovery from

anesthesia and must be considered in the analysis of the results of this study. Hooper and Qing, (1990) found another example of age-related pharmacodynamic and pharmacokinetic differences in humans. They discovered significant gender and age specific differences in the metabolism and clearance of mephobarbital. Young men cleared the drug faster than older men and faster than women of all age groups. However, elimination in elderly men was not significantly different from elderly women.

Obesity can affect the pharmacokinetics and pharmacodynamics of drugs. One important characteristic of drugs is their lipid solubility. Abernethy, Greenblatt, Divoll, & Shader, (1982) found the half-life of the lipid soluble drug, desmethyldiazepam, to be longer in obese subjects than non-obese subjects. The difference was believed to be secondary to a much larger volume of distribution for this drug in the obese patients. In contrast, Abernethy, Greenblatt, & Smith, (1981) found that the volume of distribution of digoxin was not affected by obesity, since digoxin distributes mainly to muscle tissue. Ideal body weight needs to be considered when dosing medications. For the purposes of this study anyone with a

body mass index (BMI) greater than 30% of their ideal body weight (IBW) was excluded.

The focus of this study was the effect of gender on recovery from sevoflurane and propofol anesthesia. While there is little information in the literature about gender differences in anesthesia recovery, there is considerable information on gender differences in the pharmacokinetics and pharmacodynamics of many drugs. Gender affects drug actions in many ways and the rest of this chapter will focus on these effects.

One major difference between men and women is the hormonal changes associated with menstruation. Studies have shown that differences in hormone levels during the menstrual cycle affect the pharmacokinetics and pharmacodynamics of some drugs. Nayak, Khirsagar, Desai, & Satoskar, (1988) compared the elimination of antipyrine in men and women and found that elimination was faster in women on days 15 and 21 of their menstrual cycle as compared to day 5. Male subjects did not show concentration fluctuations of antipyrine in their urine. However, Abdu-Aguye, Dunlop, Patel, & Turner, (1986) found no menstrual cycle related differences in propranolol pharmacokinetics

and Kirkwood, Moore, Hayes, DeVane, & Pelonero, (1991) found no difference in alprazolam metabolism at different stages of the menstrual cycle. The original plan of the study was to ask all females enrolled to identify the first day of their last menstrual period (LMP). The data was to be recorded on the data collection tool and analyzed against recovery times. This data was not reliably collected and no analysis was completed.

Oral contraceptive use by females must also be considered as these medications alter natural hormone levels. Roberts, Desmond, Wilkinson, & Schenker, (1979) found a small, but significant, difference in plasma binding levels of alprazolam between women on oral contraceptives and women not on oral contraceptives. The authors also found plasma protein binding differences between women who were not taking oral contraceptive steroids and men.

Liver enzymes, such as those responsible for drug metabolism, can show gender specificity and differences in these enzymes can produce differences in drug metabolism. An in vitro study of human liver CY3PA enzymes showed 24% higher activity in females over males (Hunt, Westerkam, &

Stave, 1992). Propofol is extensively metabolized in the liver whereas sevoflurane is eliminated mainly via the lung.

Plasma protein binding is important for the biologic availability and clearance of medications and some gender related differences in plasma protein binding have been found. Verbeek, Cardinal, & Wallace, (1984) found a clinically significant increase in α 1-acid glycoprotein plasma concentrations in older men while older women did not show this increase. A study by Routledge, Stargel, Kitchell, Barchowsky, & Shand, (1981) showed α 1-acid glycoprotein levels to be reduced in women compared to men and to be further reduced in women taking estrogen contraceptives. In their study, α 1-acid glycoprotein levels were inversely proportional to the level of free lidocaine in the blood.

Differences in nociception have been noted between men and women. In a study of oral surgical patients (Gear et al., 1996) treated post-operative pain with nalbuphine and butorphanol. Both of these medications primarily act at κ -opioid receptors in humans. In this study women showed more analgesic effect than men, as indicated by their responses

on a visual analog scale. The amount of medication given was adjusted for body weight. The authors believe this to be a result of gender difference in endogenous κ -opioid pain modulating pathways. Another study involving ibuprofen (Walker & Carmody, 1998) showed satisfactory pain relief in men and almost no pain relief in women. The only major pharmacokinetic difference noted was a two-fold larger volume of distribution in the female subjects. When morphine, which primarily acts at μ -opioid receptors, was compared between men and women a marked difference was observed. Morphine exhibited a slower onset in women with more potent and longer lasting effects (Sarton et al., 2000).

This study used sevoflurane and propofol for maintenance of general anesthesia. These agents have a long history of safe and effective use, but they are not perfect. Practitioners have used volatile anesthetics alone or in conjunction with IV anesthetic drugs to achieve desired effects on patients. The quest for the ideal anesthetic agent is ongoing. This ideal agent should provide rapid, smooth, and pleasant induction, facilitate maintenance of an adequate depth of anesthesia, lack intra-

operative side effects, and result in quick emergence with short recovery time without post-operative side effects (Smith, White, Nathanson, & Gouldson, 1995). Some commonly used agents come close to this ideal but do not possess all of the desired characteristics.

Sevoflurane

Sevoflurane is a methyl-isopropyl ether and has a blood-gas partition coefficient of 0.69 (Strum & Eger, 1987). This low solubility contributes to a rapid induction and emergence from anesthesia as compared to most other volatile anesthetics. It is the least pungent of the volatile agents, leading to decreased breath holding, airway irritation, excess salivation or laryngospasm (Smith et al., 1995).

A group of patients, who were premedicated with fentanyl then exposed to 5% sevoflurane with 67% nitrous oxide in oxygen, were induced in 109 seconds. There were no adverse airway events noted. In unmedicated patients, induction was even more rapid using a single vital capacity breath induction technique. The single breath technique permitted earlier loss of unconsciousness, averaging 54 seconds (Smith et al., 1995). Sevoflurane has also proven

to be an effective drug for induction of general anesthesia children. Infants lost eyelash reflex in 54 seconds, and children ages 3 to 12 lost this reflex in 76 seconds.

Anesthesia with sevoflurane has also had a low incidence of respiratory complications (Lerman, Sikich, Kleinman, & Yentis, 1994).

During maintenance of general anesthesia the degree of control over the depth of anesthesia has been defined as the difference between anesthetic concentration delivered by the vaporizer and the resultant alveolar concentration (Smith et al., 1995). The ratio of these two concentrations is determined by the degree of rebreathing by the patient and the uptake of agent by tissue. An inhaled agent with a low blood-gas coefficient will have a lower uptake than a more soluble agent, thus allowing more precise control over the anesthetic effect (Smith et al., 1995). Cardiac output is one factor that can affect the uptake and delivery of the agent. Sevoflurane is not associated with an increase in heart rate or increased myocardial consumption of oxygen (Smith et al., 1995).

The solubility of sevoflurane contributes to its fast elimination. For surgeries lasting one to four hours,

emergence with sevoflurane was 4.1 minutes, as compared with 6.7 minutes with isoflurane (Smith, Ding, & White, 1992). A multi-center trial comparing sevoflurane and isoflurane for ambulatory surgery also found that sevoflurane was associated with a faster emergence time, but the patients were not ready to be discharged any sooner than the isoflurane group (Philip, Kallar, & Bogetz, 1993).

Sevoflurane with nitrous oxide and desflurane with nitrous oxide were compared for maintenance of anesthesia in women undergoing outpatient laparoscopic sterilization procedures (Nathan, Freedman, Smith, & White, 1995). No significant differences in recovery and hospital discharge were noted.

Sevoflurane is metabolized to free fluoride and hexafluoroisopropanol. Hepatic cytochrome P450 2E1 is the main isoform responsible for sevoflurane metabolism. Patients with liver disease may have altered sevoflurane elimination (Kharasch et al., 1995).

Propofol

Propofol, an intravenous (I.V.) sedative hypnotic, is commonly used for sedation during minor surgical and diagnostic procedures as well as for induction and

maintenance of unconsciousness during general anesthesia. Propofol's rapid induction and recovery profile has made it a popular anesthetic agent in both inpatient and outpatient surgery.

Clinically important properties of propofol include rapid onset of hypnosis and unconsciousness, depression of cardiovascular and respiratory systems, decreased cerebral blood flow, and limited analgesia. Propofol has also been associated with a low incidence of postoperative nausea and vomiting (PONV) (Fredman et al., 1995).

Hypnosis, followed by unconsciousness, is rapid after administration of an intravenous bolus of propofol as the drug moves quickly from the blood to highly perfused tissues (including the brain), then to muscle, and finally fat. Propofol's high lipophilicity allows rapid penetration of the blood-brain barrier where it acts at the GABA_A receptor to increase chloride conductance, decrease neuronal excitation, and provide unconsciousness. The blood-brain equilibration half-life has been estimated at 2.9 minutes but may occur in as little as 90 seconds (Schuttler, Schwilden, & Stoeckel, 1986).

Individual sensitivity to propofol and how rapidly

propofol reaches its effect site determines how rapidly one loses consciousness (Wakeling, Zimmerman, Howell, & Glass, 1999). The onset of propofol is determined by cardiac output and volume of distribution. Volume of distribution of propofol, a highly lipophilic drug, is dependent on the amount of body fat. Women generally have a higher percent of body fat than men (Vuyk et al., 2001).

When a propofol infusion is turned off the concentration in the central compartment is higher than in the poorly perfused compartments, and redistribution continues to these sites. Once redistribution ceases propofol begins to slowly return from the peripheral to the central compartment. This slow return is manifested as a long terminal elimination half-life ($t_{1/2\beta}$), which does not appear to be clinically significant. Primary metabolism of propofol occurs rapidly in the liver and recovery from a propofol infusion is rapid (Hughes, Glass, & Jacobs, 1992).

Hughes et al., (1992) proposed the concept of context-sensitive half time to explain the elimination patterns and recovery from anesthetic agents. The half time refers to the amount of time required for the concentration of the agent in the central compartment to be reduced by one half.

Following propofol infusions of up to three hours the context sensitive half time is 25 minutes.

Propofol is a cardiovascular depressant. Hypotension following intravenous administration is common, but rebound tachycardia does not usually accompany the decrease in blood pressure. Kazama et al., (2000) found that systolic blood pressure values decreased as propofol induced sedation increased. In a study of women, Vuyk et al., (1992) found both the diastolic and systolic blood pressures decreased before hypnotic effects of propofol were noted. Wakeling et al., (1999) found an average decrease in mean arterial pressure (MAP) of 23-25% for all study participants (both men and women) receiving propofol. As well as the cardiovascular effects, induction doses of propofol effectively reduce tidal volume, depress respiration, and blunt pharyngeal reflexes. These changes facilitate endotracheal intubation (Bryson, Fulton, & Faulds, 1995).

Visser, Hassink, Bonsel, Moen, & Kalkman, (2001) found that recovery time was significantly shorter (115 minutes vs 135 minutes, $p < .001$) and postoperative nausea and vomiting (PONV) was significantly reduced in patients

receiving total intravenous anesthesia (TIVA) with propofol and air compared to isoflurane-nitrous oxide. Women were found to suffer more PONV ($p < .001$) than men in both the propofol and isoflurane groups. A study by Ebert, Robinson, Uhrich, Mackenthun, & Pichotta, (1998) found that there were no significant differences between sevoflurane and propofol with respect to recovery time or PONV. Fredman, et al (1995) reported that the use of sevoflurane for induction or maintenance of anesthesia resulted in a higher incidence of PONV when compared to propofol.

There is debate whether or not propofol possesses analgesic properties, and if it does, to what degree. In a study of 21 women undergoing lower abdominal surgery propofol was found to reduce the nociception of painful stimuli in the unconscious female patient (Vuyk et al., 1992).

Recovery from general anesthesia is dependent on the pharmacokinetic and pharmacodynamic profiles of the agents administered. Gender has been shown to affect the pharmacokinetics and pharmacodynamics of propofol. Gan et al., (1999) discovered that women unexpectedly recovered from a general anesthetic with propofol and alfentanil

significantly faster than men ($p < .05$), although there was no statistically significant difference in the drug dosages administered. Time to eye opening for women was 7.0 ± 5.2 minutes and 11.2 ± 6.23 minutes in men. Time to first response to verbal command was 8.12 ± 6.23 minutes for women and 11.67 ± 8.61 minutes for men. Reanalysis of data from Glass et al., (1997) found that women had significantly higher BIS values than men at the same propofol concentration and the propofol concentrations for women at the point of unconsciousness were significantly higher than those of men.

CHAPTER III

Methodology

Men and women have been found to respond differently to certain drugs and it is possible that this gender difference is true for all drugs. More research is needed to describe how men and women respond to general anesthesia. There also has been little research describing how gender affects overall surgical recovery time. This study attempted to determine if gender influences recovery time from sevoflurane and propofol. The anesthetic regimen for each subject was guided by a preoperative evaluation and was designed to optimize each subject's physiological and psychological state; no subject's anesthetic plan was changed to support the assumptions or purpose of the study.

The study was a descriptive, non-randomized, quasi-experimental design. In this chapter the following will be discussed: the population, sample, setting, instrumentation, data collection procedure, protection of human subjects, study design, and data analysis.

Population, Sample, and Setting

Subjects were selected from a convenience sample of adult patients presenting for non-emergent surgery to Wilford Hall Medical Center, a United States Air Force

medical treatment facility located in San Antonio, Texas. An *a priori* power analysis based on previously published data indicated that a sample size of 40 (20 in each group) was needed to detect a medium to large effect (.25) with a power of .80 and alpha at .05. Gan, Glass, & Windsor, (1997) used a sample of 96 men and 178 women with a medium effect size to show a statistically significant difference in recovery time of 3.55-4.17 minutes. While statistically significant this small increment of time is of little clinical significance. This study sought to determine if a clinically significant difference in recovery time (≥ 10 minutes) between men and women exists following general anesthesia with sevoflurane and propofol. For this study, a small sample size and medium to large effect were adequate to detect a larger time interval.

Study participants were stratified based on their stated gender. A stratified sampling schedule was used to ensure an equal number of men and women who met the following inclusion criteria: American Society of Anesthesiologist (ASA) classification I or II, aged 18-55 who underwent a non-emergent surgical procedure lasting 45-180 minutes. ASA I classification includes normal healthy

patients; ASA II patients are those with mild systemic disease that does not cause functional impairment (Morgan & Mikhail, 2002). Subjects enrolled in this study received standard of care anesthesia guided by a preoperative evaluation of their physical and psychological status.

Excluded from the study were individuals with a body mass index (BMI) $>30\%$ of their ideal body weight (IBW), those who had general anesthesia within the previous two weeks, and females who were pregnant. These factors affect the uptake, distribution, and elimination of drugs and may influence recovery time.

Instrumentation

The primary outcome variable of interest was time to recovery from general anesthesia. Recovery from general anesthesia was defined as the subject's ability to both open their eyes and grip and release the investigator's hand when instructed to do so. Eye opening and the ability to follow commands are well described in the literature as accurate measures of early recovery from general anesthesia. Smith et al., (1992) in a study involving women only, found the time from cessation of anesthetic agents to eye opening and response to simple commands to be

indicative of recovery from propofol, sevoflurane, isoflurane and/or nitrous oxide. Myles, Hunt, Fletcher, Smart, & Jackson, (2000) in a study of men and women, also used eye opening and ability to follow commands to indicate recovery from general anesthesia. The anesthetics used in their study were propofol, thiopental, sevoflurane, and isoflurane.

Data collection tool. Instruments used in this study were a data collection tool (Appendix A) and the Ohmeda 5250 Respiratory Gas Monitor. The data collection tool was an original document created by the researchers for this study; it had not previously been used. All information pertinent to the study was recorded on this instrument by a study investigator. Subject demographics recorded were height, weight, age, ASA status, surgical procedure, length of procedure, and medications administered during the intraoperative period. Medication doses and administration times, times to eye opening and hand grip/release were also recorded.

Respiratory Gas Monitor. The quantification of exhaled sevoflurane in the anesthesia circuit (end-agent concentration) was measured using the Ohmeda 5250

respiratory gas monitor (RGM). The Ohmeda 5250 RGM has a range of 0 to 8.0% ($\pm 2.0\%$), and resolution of 0.1% (Datex-Ohmeda, 2002). End agent concentrations were recorded on the data collection tool at five-minute intervals until the agent was turned off. After sevoflurane was shut off, the end-concentration was measured every one minute as described below.

Prior to the start of the study all investigators received instruction on the correct documentation procedure as well as how to assess recovery end points. A faculty member individually assessed the investigators. This instruction and subsequent observation served to insure inter-rater reliability.

Procedure for Data Collection

Demographic data was recorded on the data collection tool when the subject was met in the preoperative holding area. Baseline vitals signs (blood pressure, heart and respiratory rate, temperature) were recorded at this time. Following initial data collection the patient received standard-of-care preparation and anesthesia.

Preoperative anxiety was attenuated with midazolam 0.03-0.1 mg/kg intravenously (I.V.). Subjects were then

transferred to the operating room and placed on standard monitors. Preoxygenation was accomplished with 100% oxygen administered via facemask for five minutes.

General anesthesia was induced with propofol 2mg/kg I.V., fentanyl 2 mcg/kg I.V., and vecuronium 0.1 mg/kg I.V. If rapid sequence intubation (RSI) was required succinylcholine 1.5 mg/kg was substituted for vecuronium and appropriate aspiration prophylaxis (ranitidine 50 mg I.V., metoclopramide 10 mg I.V., and Bicitra 30 ml by mouth) was administered. All other induction drugs remained the same during RSI. The subject's trachea was intubated once adequate anesthesia was obtained as shown by standard indicators.

General anesthesia was maintained with sevoflurane delivered at a concentration to ensure adequate anesthesia. Propofol was infused intravenously at 100mcg/kg/minute. Fresh gas flow was maintained at 3L/minute and vecuronium boluses (0.8 mcg/kg I.V.) were administered as indicated to maintain adequate neuromuscular blockade. Fentanyl was administered as deemed appropriate by the anesthesia provider to insure adequate analgesia. Subjects requiring more than 3 mcg/kg/hour of fentanyl for analgesia were

removed from the study, as high doses of opioids may interfere with the recovery profile of sevoflurane and propofol.

Discontinuation of, and emergence from, general anesthesia was accomplished in the following manner. The propofol infusion was discontinued 20 minutes before the end of the case. End of the case was defined as the point when it was appropriate to extubate the patient. Sevoflurane was discontinued five minutes before the end of the case. The discontinuation of sevoflurane was recorded as time zero. At time zero fresh gas flow was increased to 10L/minute. Neuromuscular blockade was reversed with the I.V. administration of neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg.

In order to assess recovery endpoints, subjects were asked to open their eyes and grip and then release the investigators hand. Assessments were made and recorded every one minute from time zero. Recovery end points were met when the subject could open his or her eyes and grip and release the investigator's hand when asked to do so. Standard postoperative care was provided for all subjects.

Recovery data was collected and recorded by study

investigators in the following manner. Starting at time zero the investigators requested that the subject open their eyes by stating "Mr/Ms/Mrs (subject's name) open your eyes and squeeze my fingers". The investigator spoke in a conversational voice while standing at the subject's head and placed their middle and index fingers in the subject's hand. The request was repeated at one-minute intervals as indicated by the wall clock. The results of the request (eye opening/no eye opening, hand grip/no hand grip) were recorded on the data collection sheet. If handgrip was elicited, the investigator then said "Mr/Ms/Mrs (subject's name) release my fingers" in a conversational voice. Once the subject opened their eyes and gripped and released the investigator's hand the recovery endpoints were met. End-agent sevoflurane levels were also recorded at the same one-minute intervals and when the recovery end point was met.

Protection of Human Subjects

To ensure protection of the human subjects enrolled, this study was approved by the research Institutional Review Board (IRB) at Wilford Hall Medical Center. Additional subject protection was provided by obtaining

written informed consent from all those enrolled (Appendix B). Only uncompromised, adult subjects, ASA I or II, were included. Privacy and confidentiality was assured by removing identifying information from documents used in the study. Subjects were referred to by a numerical code and not identified with their name.

Study design

The study design was a descriptive, non-randomized, quasi-experimental. Study participants were stratified based on their stated gender. The sample consisted of an equal number of men and women.

The standard of care anesthesia was not adjusted to meet the anesthesia requirements of the study. Only subjects who would, as apart of their care, receive the specified anesthetic regime were included in the study.

As with any quasi-experimental design, threats to internal validity exist. In the study a selection bias was apparent because randomization of gender is not possible. Failure to randomize, risks group inequality. Additionally, an instrumentation threat may be reflected in the study. Different investigators were prompting subjects to open their eyes and grip/release the investigator's hand. Tone

of voice and volume, as well as pressure exerted during tactile stimulation may be difficult to control from one investigator to another. Instruction on how to elicit the desired responses from the subjects was given to all investigators prior to the start of the study.

Additionally, each investigator practiced eliciting responses from subjects before one observer. This observer made necessary corrections in technique to ensure all investigators elicited responses in the same manner.

Data analysis

Demographic data were analyzed using the Students t-test. The time to eye opening, handgrip and total time to recovery were analyzed using the Mann-Whitney U test.

Significance was set at 0.05 with a power of .80.

Chapter IV

Analysis of Data

Chapter IV presents the results of the statistical analysis of the collected data. SPSS® version 11.0 for Windows® was used for analysis. Prior to the start of the study all investigators received instruction on the correct documentation procedure as well as how to assess recovery end points. A faculty member assessed each investigator to ensure that each was collecting the end point data in the same manner. This instruction and subsequent observation served to insure inter-rater reliability.

Description of Sample

Fifty-four subjects were consented for this study. Four subjects were disenrolled after exceeding the parameters, leaving 24 men and 24 women completing the study. The sample consisted of 30 ASA I and 18 ASA II subjects (Table 1). Weight range was 52 - 107 kg with a mean of 76.3 kg and a SD of 14.2 kg. Procedure time ranged from 45 minutes to 180 minutes with a mean of 108 minutes (SD 36.3). Surgery type and length of surgery were also compared between men and women (Table 2). The Student's t-test was used to evaluate all demographic data. No significant differences were found.

Findings

Table 1

Gender Distribution of ASA Status and Age

Gender	ASA I	ASA II	Age Range/Average
Males	17 (56.7%)	7 (38.9%)	19-55 (31.75)
Females	13 (43.3%)	11 (61.1%)	18-51 (30.92)

Table 2

Gender Distribution of Surgery Types

Surgery	Male	Female
Oral	4	1
Orthopedic	6	3
General	6	3
Urology	4	0
ENT	4	7
Gynecologic	0	11

Surgery Type for One Subject Not Available

Time differences to eye opening, hand grip/release, and total minutes to recovery were analyzed using a Mann-Whitney U test. No statistically or clinically significant difference in recovery time was found. Table 3 shows the median data for recovery endpoints by gender.

Table 3

Median Times to Eye Opening

Gender	Minutes to eye opening	Minutes to hand grip release	Total minutes to recovery
Males	9.0	9.5	9.5
Females	7.5	8.0	8.0

Chapter V

Discussion, Conclusions, Implications, Recommendations

This study was conducted to determine if gender affected the recovery time from sevoflurane and propofol general anesthesia. Historically, women have not been included in human pharmacologic research and little is known about gender differences in recovery time from general anesthesia. This study was designed to determine if men and women recovered at different rates and, if so, was the difference large enough to warrant consideration in military contingency planning.

The remainder of this chapter includes a discussion of the results in light of the research findings of others, the conclusions drawn from this study, implications for nursing, and recommendations for further research.

Discussion

The research question for this study was "Does gender affect recovery time from general anesthesia with propofol and sevoflurane?" The assumption of this study was "Recovery time from general anesthesia is effected by gender-unique differences in pharmacokinetics and pharmacodynamics." Differences in recovery times were determined by measuring time to hand grip and eye opening.

Based on discussions with military anesthetists and recovery personnel, an average 10-minute difference in recovery time was felt to be clinically important. This ten-minute difference could improve turnover times and reduce PACU congestion. This study failed to find any significant difference in recovery time.

The theoretical framework for the study was the theory of consciousness. Hand grip and eye opening were used as an indicator of return to consciousness. Since no significant differences in time to hand grip or eye opening, were found, no differences in time to recovery can be inferred from the sample data. The sample data does not support the assumption that gender differences in pharmacokinetics and pharmacodynamics are manifested as a difference in recovery time from sevoflurane and propofol anesthesia. There are several possible reasons why there was no observed difference in recovery times. The combination of sevoflurane with propofol may have masked any differences that would have been seen if either had been used alone. Hand grip and eye opening may not have been sensitive enough indicators to detect a small difference in recovery. This study did not account for other factors such as

patient temperature at the end of surgery. Metabolism of anesthetic drugs is affected by temperature. Hypothermic patients metabolize drugs slower than normothermic or hyperthermic patients. If one group was, on average, colder than the other at time of recovery then speed of emergence may have been affected. Finally, there may simply not be a difference in how men and women recover from general anesthesia.

This study does not support the findings of Gan et al., (1999) or Myles et al., (2001). Both of these studies showed a significantly shorter time to recovery for women versus men after general anesthesia. Gan's study used propofol, nitrous oxide and alfentanil for anesthetics. The lack of a volatile agent and the use of a shorter-acting opioid in Gan's study make it very different from this study. This difference alone makes it difficult to draw any conclusions from the results. Also, Gan and Myles' sample demographic included elderly subjects. This study included no subject over age 55. As discussed above, age can have various effects on the pharmacokinetics and pharmacodynamics of drugs. Age-related differences in drug metabolism could account for some of the differences in the

findings. Myles and Gan included ASA III patients in their studies. ASA III patients, by definition, have systemic disease processes that limit functioning. The disease processes, and the patient's routine medications, may alter anesthetic drug metabolism and account for the different results.

This study had several limitations. First, the protocol was not flexible enough regarding the amounts of fentanyl and vecuronium that could be used. This made staying within the protocol and administering a proper anesthetic difficult, but not impossible. For example the protocol called for a propofol infusion at 100mg/kg/min until 20 minutes before the end of surgery. After discontinuing the propofol infusion, the sevoflurane was continued until five minutes before the end of surgery. The discontinuation of sevoflurane was recorded as time zero. Recovery end-point measurements were started at time zero. Predicting exactly when the surgery would end was very difficult, so propofol was sometimes turned off too late or too early. If propofol was turned off too early, sevoflurane levels had to be increased to maintain adequate depth of anesthesia. If the propofol was discontinued too

late, which was usually the case, recovery was extended for both genders, and room turnover was delayed. A more clinically realistic protocol would have been to reverse the order of drug discontinuation. Sevoflurane would be discontinued approximately 20 minutes before the end of the case, and propofol five minutes before the end of the case.

Additionally there were differences in emergence techniques. Some subjects were allowed to breathe spontaneously towards the end of the case and some were mechanically ventilated until the end. The emergence technique used was chosen by the preceptor who was in charge of the case. Different emergence techniques may play a role in how quickly patients recover from general anesthesia, however, this difference was not analyzed. Also, injection of local anesthetics into the wound by the surgeon at the end of the case was not analyzed in this study. Some subjects received local anesthetics and some did not. A patient having less pain at the end of surgery may reach the study recovery end points more slowly than one experiencing a painful stimulus. As noted, no record was made regarding the status of the female's menstrual cycle. Hormonal differences may affect the pharmacokinetics

and pharmacodynamics of different drugs which could alter recovery from anesthesia.

Additionally, the type of surgery (gynecological, orthopedic, etc.) could have an impact on recovery times. A surgery that is more stimulating may require the administration of higher concentrations of sevoflurane or fentanyl. While the total narcotic dose remained within the study parameters it is possible that patients who receive more of these agents will awaken slower than others.

Conclusions

Based on the results of this study, there is no statistically or clinically significant gender difference in recovery time from sevoflurane and propofol general anesthesia.

Implications for Nursing

Nurse anesthetists do not need to alter their anesthetic technique using sevoflurane and propofol to plan for recovery of their patients based on gender alone. Although every patient needs an individualized plan of care, gender does not appear to be a factor in recovery given the circumstances studied.

Recommendations for Further Research

Studying sevoflurane and propofol independently may be useful if any gender differences in recovery can be found.

Additional research is needed to detect gender-based differences in the pharmacokinetics and pharmacodynamics of other drugs used in anesthesia.

APPENDIX A

Data Collection Tool

DATA COLLECTION TOOL					
Gender Differences in Recovery Times with Sevoflurane and Propofol infusion					
Demographic data:					
Random number assignment:					
Age:	Height:	in	Weight:	Kg	BMI: kg/m ² Sex: M F
ASA Classification: I II III IV			Surgical Procedure:		
Preoperative Information:					
Midazolam:		mg total/	mg/kg dose		
Adjuvant medication and doses:					
Intraoperative Information:					
Propofol total induction dose: 1-2mg/kg - mg			Fentanyl total induction dose: 0.5- 2mcg/kg - mcg		
Propofol total dose: 100mcg/kg.min			Fentanyl total supplemental dose:		
Vecuronium total dose: .08-.1mg/kg			RSI: yes no Succinylcholine total dose:		
Average end tidal sevoflurane concentration:					
Adjuvant medication and doses:					
Outcome Criteria Data:					
Time zero: sevoflurane off			End tidal sevoflurane concentration:		
Time to opening of eyes: minutes			End tidal sevoflurane concentration:		
Time to hand grip and release: minutes			End tidal sevoflurane concentration:		
Total time in minutes from time zero to meeting recovery criteria:					
Investigator:			Data collector		

Page 2

[illegible][illegible][illegible][illegible][illegible]

APPENDIX B

Informed Consent Document

7/12/02(*Gender Differences in Recovery from Propofol and Sevoflurane Anesthesia*)

BROOKE ARMY MEDICAL CENTER/WILFORD HALL MEDICAL CENTER
INFORMED CONSENT DOCUMENT
(ICD Template Version 4. Feb 02)

Gender Differences in Recovery from Propofol and Sevoflurane Anesthesia

PRINCIPAL INVESTIGATORS – Lt Col Elizabeth J Bridges, USAF NC
Capt Sean Strait, USAF, NC

If you choose not to participate in this research study, your decision will not affect your eligibility for care or any other benefits to which you are entitled.

DESCRIPTION/PURPOSE OF RESEARCH

You are being asked to consider participation in this research study. The purpose of this study is to determine if there is a difference in the amount of time it takes you to wake-up after you receive general anesthesia (medications usually given during surgery to make you unconscious) based on whether you are a man or a woman.

This study will enroll approximately 48 subjects at Wilford Hall Medical Center.

Participation in this study, will not involve any additional hospital visits.

You have been selected to participate in this study because: 1) you are scheduled to have surgery requiring general anesthesia, 2) you height and weight match what the researchers are looking for and you have not had anesthesia within the past two weeks.

PROCEDURES:

As a participant, you will undergo the following procedures: You will receive routine care before during and after your surgery. There will not be any differences in your care as a result of your participation in this study except that the investigators will measure the amount of time it takes for you to wake up from anesthesia by asking you to open your eyes and to squeeze and release their hand.

For Protocol Office Use Only:
FWH20020108H, Bridges, ICD, 25 Jun 02

WHMC INSTITUTIONAL REVIEW BOARD

25 Jun 02

Date ICD
Approved by IRB

28 Jun 03

Date ICD Expires

7/12/02(Gender Differences in Recovery from Propofol and Sevoflurane Anesthesia)

Participation in this study will not affect the type of anesthesia you will receive during your surgery. All decisions about your anesthesia will first be approved by a staff Anesthesiologist (anesthesia doctor) or Certified Nurse Anesthetist (anesthesia nurse), who is not part of the research team.

If you need a procedure requiring additional informed consent, a separate consent form will be given to you before that procedure.

RISKS OR DISCOMFORTS:

There is no known risk associated with this study. However, there may also be unforeseen risks associated with this study.

BENEFITS:

There is no guarantee you will receive any benefit from this study other than knowing that the information may help future patients.

PAYMENT (COMPENSATION)

You will not receive any compensation (payment) for participating in this study.

ALTERNATIVES TO PARTICIPATION:

Choosing not to participate in this study is your alternative to volunteering for the study.

CONFIDENTIALITY OF RECORDS OF STUDY PARTICIPATION:

Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C. 552a, and its implementing regulations. DD Form 2005, Privacy Act Statement- Military Health Records, contains the Privacy Act Statement for the records.

By signing this consent document, you give your permission for information gained from your participation in this study to be published in medical literature, discussed for educational purposes, and used generally to further medical science. You will not be personally identified; all information will be presented as anonymous data.

Your records may be reviewed by the U.S. Food & Drug Administration (FDA), other government agencies, and the WHMC Institutional Review Board.

Complete confidentiality cannot be promised, particularly for military personnel, because information

For Protocol Office Use Only:
FWH20020108H, Bridges, ICD, 25 Jun 02

WHMC INSTITUTIONAL REVIEW BOARD

25 Jun 02

Date ICD
Approved by IRB

24 Jun 03

Date ICD Expires

7/12/02(Gender Differences in Recovery from Propofol and Sevoflurane Anesthesia)

regarding your health may be required to be reported to appropriate medical or command authorities.

ENTITLEMENT TO CARE:

In the event of injury resulting from this study, the extent of medical care provided is limited and will be within the scope authorized for Department of Defense (DoD) health care beneficiaries.

Your entitlement to medical and dental care and/or compensation in the event of injury is governed by federal laws and regulations, and if you have questions about your rights as a research subject or if you believe you have received a research-related injury, you may contact the

Wilford Hall Clinical Research Squadron Commander, (210) 292-7069 or Wilford Hall Medical Center Risk Manager, 210-292-6004.

BLOOD & TISSUE SAMPLES:

No blood or tissue samples will be taken as part of this study.

VOLUNTARY PARTICIPATION:

The decision to participate in this study is completely voluntary on your part. No one has coerced or intimidated you into participating in this project. You are participating because you want to. The Principal Investigator or one of his/her associates has adequately answered any and all questions you have about this study, your participation, and the procedures involved. If significant new findings develop during the course of this study that may relate to your decision to continue participation, you will be informed.

You may withdraw this consent at any time and discontinue further participation in this study without affecting your eligibility for care or any other benefits to which you are entitled. Should you choose to withdraw, you must notify the investigator. The investigator of this study may terminate your participation in this study at any time if he/she feels this to be in your best interest.

CONTACT INFORMATION:**Principal Investigator (PI)**

The principal investigator or a member of Clinical Research Squadron staff will be available to answer any questions concerning procedures throughout this study.

Principal Investigator: Lt Col Elizabeth Bridges or Capt

Phone: (210) 292-7142

For Protocol Office Use Only:
FWH20020108H, Bridges, ICD, 25 Jun 02

WHMC INSTITUTIONAL REVIEW BOARD

25 JUN 02

Date ICD
Approved by IRB

24 JUN 03

Date ICD Expires

*7/12/02(Gender Differences in Recovery from Propofol and Sevoflurane Anesthesia)***Institutional Review Board (IRB)**

The WHMC Institutional Review Board (IRB), the hospital committee responsible for safeguarding your rights as a research subject, has assigned a member of the IRB, who is not part of the study team, to serve as an outside monitor for this study (this person is the Medical Monitor). If you have any questions about your rights as a research subject or any other concerns that can not be addressed by the PI, you can contact the medical monitor, Joseph Schmelz, PhD, RN at (210) 292-5687. Or mail to: 59th Clinical Research Squadron/MSRP, 1255 Wilford Hall Loop, Lackland Air Force Base, Texas 78230.

In addition, if you have any comments, questions, concerns or complaints, you may also contact the Chairperson of the IRB, at (210) 292-7558. Or mail to: 59th Medical Wing/CM, 2200 Bergquist Drive, Lackland Air Force Base, Texas 78230.

Your consent to participate in this study is given on a voluntary basis. All oral and written information and discussions about this study have been in English, a language in which you are fluent.

A copy of this form has been given to you.

VOLUNTEER'S SIGNATURE

VOLUNTEER'S SSN

DATE

VOLUNTEER'S PRINTED NAME

FMP

SPONSOR'S SSN

DOB

VOLUNTEER'S ADDRESS (street, city, state, zip)

ADVISING INVESTIGATOR'S SIGNATURE

DATE

(PHONE NUMBER)

For Protocol Office Use Only:
FWH20020108H, Bridges, ICD, 25 Jun 02

WHMC INSTITUTIONAL REVIEW BOARD

Date ICD
Approved by IRB

Date ICD Expires

7/12/02(Gender Differences in Recovery from Propofol and Sevoflurane Anesthesia)

PRINTED NAME OF ADVISING INVESTIGATOR

WITNESS' SIGNATURE
(Must witness ALL signatures)

DATE

PRINTED NAME OF WITNESS

TITLE OF STUDY: Protocol #:
Date Protocol Approved by WHMC/BAMC IRB:
Date(s) ICD Changes Approved by WHMC/BAMC IRB:

Subject's Stamp Plate
PRIVACY ACT OF 1974 APPLIES.
DD FORM 2005 FILED IN MILITARY HEALTH RECORDS

For Protocol Office Use Only:
FWH20020108H, Bridges, ICD, 25 Jun 02

WHMC INSTITUTIONAL REVIEW BOARD

25 Jun 02
Date ICD
Approved by IRB

24 Jun 03
Date ICD Expires

References

Abdu-Aguye, I., Dunlop, D., Patel, P., & Turner, P. (1986). Propranolol pharmacokinetics during the menstrual cycle. Postgraduate Medical Journal, 62, 1093-1095.

Abernethy, D., Greenblatt, D., & Smith, T. (1981). Digoxin disposition in obesity: Clinical pharmacokinetic investigation. American Heart Journal, 102, 740-744.

Abernethy, D., Greenblatt, D., Divoll, M., & Shader, R. (1982). Prolongation of drug half-life due to obesity: Studies of desmethyldiazepam (Clorazepate). Journal of Pharmaceutical Sciences, 71(6), 942-944.

Belerle, I., Meibohm, B., & Derendorf, H. (1999). Gender differences in pharmacokinetics and pharmacodynamics. International Journal of Clinical Pharmacology and Therapeutics, 37(11), 529-547.

Bryson, H., Fulton, B., & Faulds, D. (1995). Propofol. An update of its use in anesthesia and conscious sedation. Drugs, 50(3), 513-559.

Collins, L., Bevan, J., Bevan, D., Villar, G., Kahwaji, R., Smith, M., & Donati, F. (2000). The prolonged duration of rocuronium in Chinese patients. Anesthesia and Analgesia, 91(6), 1526-1530.

Domino, K., Posner, K., Caplan, R., & Cheney, F. (1999). Awareness during anesthesia: A closed claims analysis. Anesthesiology, 90, 1053-1061.

Ebert, T., Robinson, B., Urich, T., Mackenthun, A., & Pichotta, P. (1998). Recovery from sevoflurane anesthesia: A comparison with isoflurane and propofol anesthesia. Anesthesiology, 89(6), 1524-1531.

Fredman, B., Nathanson, M., Smith, I., Wang, J., Klein, K., & White, P. (1995). Sevoflurane for outpatient anesthesia: A comparison with propofol. Anesthesia & Analgesia, 81(4), 823-828.

Gan, T., Glass, P., & Windsor, A. (1997). Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. Anesthesiology, 87, 808-815.

Gan, T., Glass, P., Sigl, J., Sebel, P., Payne, F., Rosow, C., & Embree, P. (1999). Women emerge from general anesthesia with propofol/alfentanil/nitrous oxide faster than men. Anesthesiology, 90, 1283-1287.

Gear, R., Gordon, N., Heller, P., Paul, S., Miakowski, C., & Levine, J. (1996). Gender differences in the analgesic response to the kappa-opioid pentazocine. Neuroscience Letters, 205, 207-209.

Glass, P., Bloom, M., Kearse, L., Rosow, C., Sebel, P., & Manberg, P. (1997). Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology, 86, 836-847.

Greenblatt, D., Abernathy, D., Locniskar, A., Harmatz, J., Limjuco, R., & Shader, R. (1984). Effects of age, gender, and obesity on midazolam kinetics. Anesthesiology, 61, 27-35.

Harris, R., Benet, L., & Schwartz, J. (1995). Gender effects in pharmacokinetics and pharmacodynamics. Drugs, 50(2), 222-239.

Hooper, W., & Qing, M. (1990). The influence of age and gender on the stereo selective metabolism and pharmacokinetics of mephobarbital in humans. Clinical Pharmacology Therapy, 48(6), 633-640.

Hughes, M., Glass, P., & Jacobs, J. (1992). Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. Anesthesiology, 76, 334-341.

Hunt, C., Westerkam, W., & Stave, G. (1992). Effect of age and gender on activity of human hepatic CY3PA. Biochemical Pharmacology, 44(2), 275-283.

Kazama, T., Takeuchi, K., Ikeda, K., Ikeda, T., Kikura, M., Iida, T., Suzuki, S., Hanai, H., & Soto, S. (2000). Optimal propofol plasma concentration during upper gastrointestinal endoscopy in young, middle-aged, and elderly patients. Anesthesiology, 93, 662-669.

Keating, K., Giblin, L., Lynch, P., Quane, K., Lehane, M., Heffron, J., & McCarthy, T. (1997). Detection of a novel mutation in the ryanodine receptor gene in an Irish malignant hyperthermia pedigree: Correlation of the IVCT response with the affected and unaffected haplotypes. Journal of Medical Genetics, 34(4), 291-296.

Kharasch, E., Armstrong, A., Gunn, K., Artu, A., Cox, K., & Karol, M. (1995). Clinical sevoflurane metabolism and disposition: The role of cytochrome P4502E1 in fluoride and hexafluoroisopropanol formulation. Anesthesiology, 82, 1379-1388.

Kirkwood, C., Moore, A., Hayes, P., DeVane, C., & Pelonero, A. (1991). Influences of menstrual cycle and gender on alprazolam pharmacokinetics. Clinical Pharmacology Therapy, 50(4), 404-409.

Lerman, J., Sikich, N., Kleinman, S., & Yentis, S. (1994). The pharmacology of sevoflurane in infants and children. Anesthesiology, 80, 814-824.

Merkatz, R., Temple, R., Sobel, S., Feiden, K., & Kessler, D. (1993). Women in clinical trials of new drugs: A change in food and drug administration policy. The New England Journal of Medicine, 329(4), 292-296.

Miller, K. & Alifimoff, J. (1998). Mechanism of action of general anesthetics. In Longnecker, D., Tinker, J., & Morgan, G. (Eds.), Principles and practice of anesthesiology (2nd ed., pp. 1103-1122). St Louis: Mosby.

Morgan, G. & Mikhail, M. (2002). Clinical anesthesiology (3rd ed.). New York: McGraw-Hill.

Myles, P., McLeod, A., Hunt, J., & Fletcher, H. (2001). Sex differences in speed of emergence and quality of recovery after anesthesia: cohort study. British Medical Journal, 322(7288), 710-711.

Myles, P., Hunt, J., Fletcher, H., Smart, J., & Jackson, T. (2000). Part 1: Propofol, thiopental, sevoflurane, and isoflurane--a randomized controlled trial of effectiveness. Anesthesia and Analgesia, 91(5), 1163-1169.

Nathan, M., Freedman, B., Smith, I., & White, P. (1995). Sevoflurane versus desflurane for outpatient anesthesia: A comparison of maintenance and recovery profiles. Anesthesia & Analgesia, 81, 1186-1190.

Nayak, V., Khirsagar, N., Desai, N., & Satoskar, R. (1988). Influences of menstrual cycle on antipyrine pharmacokinetics in healthy Indian female volunteers. British Journal of Clinical Pharmacology, 26, 604-606.

Ortolani, O., Conti, A., Sall, B., Sallers, J., Diouf, E., Kane, O., Roberts, S., & Novelli, G. (2001). The recovery of Sengalese African Blacks from intravenous anesthesia with propofol and remifentanyl is slower than that of Caucasians. Anesthesia & Analgesia, 93(5), 1222-1226.

Pasternak, L. (1998). Outpatient Anesthesia. In Longnecker, D., Tinker, J., & Morgan, G. (Eds.), Principles and practice of anesthesiology (2nd ed., pp. 2223-2265). St Louis: Mosby.

Pavlin, D., Rapp, S., Polissar, N., Malmgren, J., Koerschgen, M., & Keyes, H. (1998). Factors affecting discharge time in adult outpatients. Anesthesia & Analgesia, 87, 816-826.

Peduto, V., Mezzetti, D., Properzi, M., & Giorgini, C. (2000). Sevoflurane provides better recovery than propofol. European Journal of Anesthesiology, 17(2), 138-143.

Philip, B., Kaller, S., & Bogetz, M. (1993). Multicenter comparison of sevoflurane with isoflurane in nitrous oxide for ambulatory surgery. Anesthesiology, 78, 78-79.

Pugh, M. (Ed.). (2000). Stedman's medical dictionary (27th ed.). Philadelphia: Lippincott, Williams, & Wilkins.

Roberts, R., Desmond, P., Wilkinson, G., & Schenker, S. (1979). Disposition of chlordiazepoxide: Sex differences and effects of oral contraceptives. Clinical Pharmacology Therapy, 25(6), 826-831.

Routledge, P., Stargel, W., Kitchell, B., Barchowsky, A., & Shand, D. (1981). Sex related difference in plasma protein binding of lignocaine and diazepam. British Journal of Clinical Pharmacology, 11(3), 245-250.

Sarton, E., Olofsen, E., Romberg, R., den Hartigh, J., Kest, B., Nieuwenhuijs, D., Burm, A., Teppema, L., & Dahan, A. (2000). Sex differences in morphine analgesia: An experimental study in healthy volunteers. Anesthesiology, 93, 1245-1254.

Schuttler, J., Schwilden, H., & Stoeckel, H. (1986). Pharmacokinetic-dynamic modeling of Diprivan. Anesthesiology, 65, 549.

Seaber, E., Lipitrol, J., On, N., Dixon, R., Seaber, E., Chillick, G., Posner, J., Rolan, P., & Pack, R. (1997). The absolute bioavailability and metabolite disposition of the novel antimigraine compound Zolmitriptan. British Journal of Clinical Pharmacology, 43(20), 579-587.

Shafer, S. (1998). Principles of pharmacokinetics and pharmacodynamics. In Longnecker, D., Tinker, J., & Morgan, G. (Eds.), Principles and practice of anesthesiology (2nd ed., pp. 1150-1210). St Louis: Mosby.

Smith, I., Ding, Y., & White, P. (1992). Comparison of induction, maintenance, and recovery characteristics of sevoflurane-nitrous oxide and propofol-sevoflurane-nitrous oxide with propofol-isoflurane-nitrous oxide anesthesia. Anesthesia & Analgesia, 74, 253-259.

Smith, I., White, P., Nathanson, M., & Gouldson, R. (1995). The role of sevoflurane in outpatient anesthesia. Anesthesia & Analgesia, 81(6), 67-72.

Song, D., Girish, P., & White, R. (1998). Fast-track eligibility after ambulatory anesthesia: A comparison of desflurane, sevoflurane, and propofol. Anesthesia & Analgesia, 86, 267-273.

Stedman, T. (Ed.). (2002). Stedman's Medical Dictionary (27th ed.). Philadelphia: Lippincott, Williams, & Wilkins.

Strum, D., & Eger, E. (1987). Partition coefficients for sevoflurane in human blood, saline, and olive oil. Anesthesia and Analgesia, 66, 654-656.

Thomas, C. (Ed.). (1989). Taber's Cyclopedic Medical Dictionary (16th ed.). Philadelphia: F.A. Davis Company.

Verbeek, R., Cardinal, J., & Wallace, S. (1984). Effects of age and sex on the plasma binding of acidic and basic drugs. European Journal of Clinical Pharmacology, 27, 91-97.

Visser, K., Hassink, E., Bonsel, G., Moen, J., & Kalkman, C. (2001). Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane--nitrous oxide: Postoperative nausea and vomiting and economic analysis. Anesthesiology, 95(3), 616-626.

Vuyk, J., Engbers, F., Lemmens, H., Burm, A., Vletter, A., Gladines, M., & Bovill, J. (1992). Pharmacodynamics of propofol in female patients. Anesthesiology, 77, 3-9.

Vuyk, J., Oostwouder, C., Vletter, A., Burm, G., & Bovill, J. (2001). Gender differences in the pharmacokinetics of propofol in elderly patients during and after continuous infusion. British Journal of Anesthesia, 86(2), 183-188.

Wakeling, H., Zimmerman, J., Howell, S., & Glass, P. (1999). Targeting effect compartment or central compartment concentration of propofol. Anesthesiology, 90(1), 92-97.

Walker, J., & Carmody, J. (1998). Experimental pain in healthy human subjects: Gender differences in nociception and response to ibuprophen. Anesthesia and Analgesia, 86, 1257-1262.

Young, G., & Pigott, S. (1999). Neurobiological basis of consciousness. Archives of Neurology, 56(2), 153-157.

VITA

Sean Strait was born [REDACTED] in Fort Dodge, Iowa. He was raised on a dairy farm and graduated with honors from Gilmore City-Bradgate High School. After graduation, Sean enlisted in the United States Army where he was trained as a paratrooper. After serving four years in the 82nd Airborne division, Sean returned to Iowa to attend college and serve in the Army reserves. Sean graduated with a Bachelors in Science of Nursing Degree in 1996 and was commissioned into the United States Air Force Nurse Corp in 1997. After serving as an emergency and trauma nurse Sean was accepted for graduate training in nurse anesthesia. He will complete his training in December, 2003. Sean is married with two children.

VITA

Dino Raul Dominguez was born in New York, New York on [REDACTED], the son of [REDACTED] and [REDACTED]. After completing his work at St. Francis Preparatory High School, in 1990, he entered The State University of New York at Stony Brook. In 1993 he transferred to Florida State University, where he received the degree of Bachelor of Science in Nursing in December 1996. During the following years he was active duty in the United States Air Force. In June 2001 he entered the United States Army Graduate Program in Anesthesia Nursing in San Antonio, Texas. In April 1998 he married [REDACTED] of Columbia, Maryland. One daughter, [REDACTED] was born in [REDACTED].

VITA

Donna Gunning was born in Harlan, Kentucky to [REDACTED] and [REDACTED] on [REDACTED]. Following high school graduation she entered the U.S. Air Force and served as a medical technician for eight years. After leaving the Air Force, Donna completed a Bachelor of Science degree in Nursing in 1995 from the University of North Dakota. Donna was commissioned in the Air Force in the summer of 1995 and has served on active duty since that time. She enrolled in the U. S. Army Graduate Program in Anesthesia Nursing in June 2001. She will complete the requirements for a Master of Science in Nursing degree in December 2003. Donna has two children, [REDACTED] and [REDACTED].

This thesis was typed by Sean A. Strait